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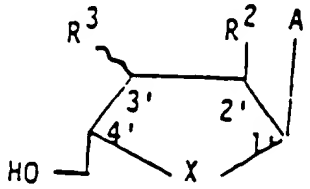
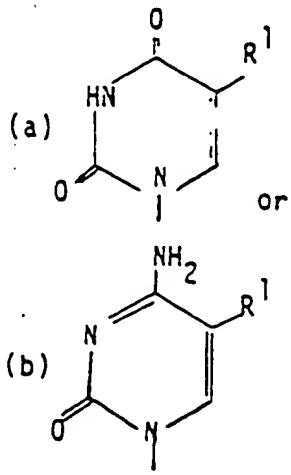
(54) Title: NUCLEOSIDES AND NUCLEOSIDE ANALOGUES, PHARMACEUTICAL COMPOSITION AND PROCESSES FOR THE PREPARATION OF THE COMPOUNDS

(I)





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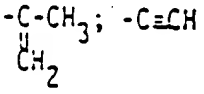


(57) Abstract

A compound of formula (I), wherein the radicals A, X, R^1, R^2, and R^3 are defined as follows: A: formula (a) or formula (b); X: (a) O; (b) S; (c) CH_2; R^1: H; alkyl containing 1-3 carbon atoms; $-CH=CH_2$; $-CH=CH-CH_3$; $-CH_2-CH=CH_2$; formula (II); $-C\equiv CH$; R^2: H; or R^2 constitutes together with R^3 a carbon-carbon bond; R^3: H; F; Cl; Br; I; N_3; CN; $C\equiv CH$; OH; OCH_3; CH_2OH; and when R^3 is F; Cl; Br; I; N_3; CN; $C\equiv CH$; OH; OCH_3 or CH_2OH it may have either the cis-configuration or trans-configuration relative to the hydroxymethyl function at position 4', or R^3 constitutes together with R^2 a carbon-carbon bond, and therapeutically acceptable salts thereof, for use in therapy, in particular for the treatment of HIV virus infections.

Nucleosides and nucleoside analogues, pharmaceutical composition and processes for the preparation of the compounds

Field of the invention

The present invention relates to the use of chemical compounds and physiologically acceptable salts thereof for the therapeutic and prophylactic control and treatment of the Acquired Immuno Deficiency Syndrome (AIDS), infections by Human Immunodeficiency Virus, hepatiti: virus infections and retrovirus infections and method for such contro and treatment in animal and man.

Background of the invention

In the late seventies a new disease was reported, which subsequently w referred to as Acquired Immuno Deficiency Syndrome (AIDS). It is now generally accepted that a retrovirus referred to as HIV (Human Immunodeficiency Virus), formerly known as Human T-cell Lymphotropic Virus (HTLV-III) or Lymphadenopathy Associated Virus (LAV) plays an essentia role in the etiology of AIDS.

AIDS is characterized by a profound immunodeficiency due to low number of a subset of lymphocyte-T-helper cells, which are one target for HIV infection. The profound immunodeficiency in AIDS patients makes these patients highly susceptible to a variety of opportunistic infections of bacterial, fungal, protozoal or viral etiology. The etiological agents among viral opportunistic infections are often found in the herpes viru group, i.e., Herpes simplex virus (HSV), Varicella Zoster virus (VZV), Epstein-Barr virus (EBV) and, especially, cytomegalovirus (CMV). Other retroviruses affecting humans are HTLV-I and II and examples of retroviruses affecting animals are feline leukemia virus and equine infectio anaemia virus.

Hepatitis B virus infections cause severe disease such as acute hepatitis, chronic hepatitis, fulminant hepatitis in a considerable number of persons. It is estimated that there are 200 million patients with chronic hepatitis B infection in the world. A considerable number of th

chronic cases progress to liver cirrosis and liver tumours. In some cases the hepatitis infections also take a rapid and severe course as fulminant B hepatitis with about 90 % mortality. At present there is known effective treatment against hepatitis B infections.

General outline of the invention

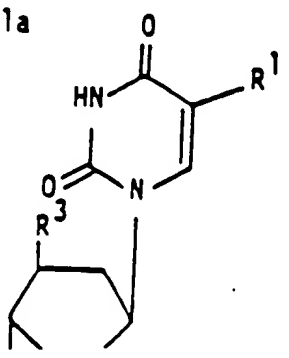
A great number of nucleoside analogues exhibit several antimetabolic activities. They do so by substituting for or competing with the natu rally occuring nucleosides. Recently some nucleoside analogues have b described, which inhibit in cell culture the multiplication of human immunodeficiency virus (HIV, also called HTLV-III, LAV), the causativ agent of AIDS and AIDS-related complex (ARC). Such compounds are for example azidothymidine, dideoxycytidine and dideoxyadenosine. These a other described HIV-antimetabolic nucleoside analogues have the same geometric relationship between the nucleoside base and the glycosidic part as the naturally occuring nucleosides, i.e. they are β-anomers.

We have now, surprisingly, found that some nucleosides and nucleoside analogues with the opposite geometric configuration, α-anomers, are potent inhibitors of HIV multiplication but not of cell-division. Anti-HIV activities are displayed by such geometric isomers which hav been modified either in the nucleoside base part, the glycoside part in both parts. The structures of these compounds are disclosed in thi invention.

Prior Art

The following compounds of the formula I below are known:

1. Compounds of the formula



wherein R^3 is OH and R^1 is as follows:

R^1 is H and CH_3: T. Nishimura, B. Shinizu, I. Iwai
Chem. Pharm. Bull. (Tokyo) 12 (1964), 1471

R^1 is C_2H_5: M. Swierkowski, D. Shugar
J. Med. Chem. 12 (1969), 533

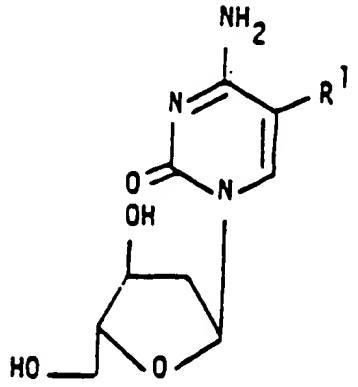
R^1 is n-C_3H_7: A. Szaboles, J. Sági, L. Ötvös
J. Carbohydrates, Nucleosides, Nucleotides 2 (1975), 197 - 211

R^1 is i-C_3H_7: M. Draminski, A. Zgit-Wroblewska
Polish J. Chemistry 54 (1980), 1085

R^1 is C≡CH: P.J. Barr, A.S. Jones, P. Serafinowski, R. Walker
J. Chem. Soc. Perkin I (1978), 1263 - 1267

and wherein R^3 is N_3 and R^1 is CH_3: M. Imezawa, F. Eckstein, J. Org. Chem. 43 (1978), 3044-3048.

2. The compound of the formula



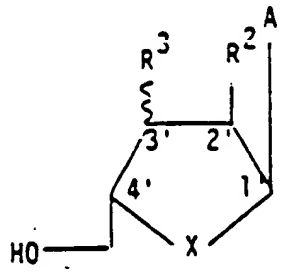
R^1 is C≡CH is described by P.J. Barr, A.S. Jones, P. Serafinowski, R. Walker, J. Chem. Soc. Perkin I (1978), 1263 - 1267

R^1 is H is described by J.J. Fox, N.C. Yung, I. Wempen and M. Hoffer. J. Am. Chem. Soc., Vol. 83 (1961), 4066-4070.

Both groups 1. and 2. concern only compounds having the 3'group and t 4'hydroxymethyl group in a trans-configuration.

Disclosure of the invention

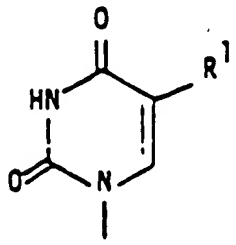
It has been found according to the present invention that the compour of the formula



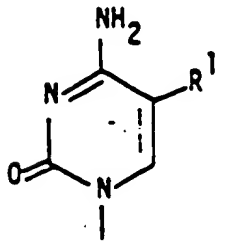
I

wherein the radicals A, X, R^1, R^2 and R^3 are defined as follows:

A: (a)



(b)



X: (a) O
(b) S
(c) CH_2

R^1: H; alkyl containing 1-3 carbon atoms;
$-CH=CH_2$; $-CH=CH-CH_3$; $-CH_2-CH=CH_2$; $-\overset{\overset{CH_2}{\|}}{C}-CH_3$; $-C\equiv CH$

R^2: H; or R^2 constitutes together with R^3 a carbon-carbon bond

R^3: H; F; Cl; Br; I; N_3; CN; $-C\equiv CH$; OH; OCH_3; CH_2OH;
or R^3 constitutes together with R^2 a carbon-carbon bond,

and therapeutically acceptable salts thereof, inhibit the multiplication of human immunodeficiency virus (HIV). The compounds of the formula I are useful as therapeutic and/or prophylactic agents in the control and treatment of HIV virus infections in mammals and man.

In a more general aspect, the compounds of the formula I are useful as therapeutic and/or prophylactic agents in the control and treatment of infections caused by retroviruses and hepatitis B virus in mammals and man.

All retroviruses, including HIV, require the enzyme reverse transcriptase in their natural cycle of replication.

Hepatitis B virus (HBV) is a DNA virus with a unique circular double-stranded DNA genome which is partly single-stranded. It contains a specific DNA polymerase required for viral replication. This DNA polymerase also acts as a reverse transcriptase during the replication of HBV DNA via an RNA intermediate.

The compounds of the formula I inhibit the activity of reverse transcriptase of retroviruses including HIV as well as the activity of DNA polymerase of hepatitis B virus.

The present invention has several aspects:

1. the novel compounds included in the formula I,

2. pharmaceutical compositions comprising a compound of the formula as active ingredient,

3. a compound of the formula I for use in therapy,

4. a compound of the formula I for use in the manufacture of a medi ment for therapeutic and/or prophylactic treatment of infections caused by a retrovirus, including HIV, or by hepatitis B virus,

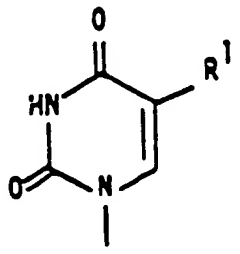
5. a method for the therapeutic and/or prophylactic treatment of in tions in mammals and man caused by retrovirus including HIV or h titis B virus, by administering to a host in need of such treatm an efficient amount of a compound of the formula I.

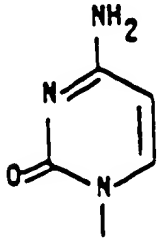
It is a preferred aspect of the invention to combat HIV virus infect in man.

The expression "alkyl containing 1-3 carbon atoms" for the radical R^1 means CH_3, C_2H_5, $CH_2CH_2CH_3$, $CH(CH_3)_2$ and cyclopropyl.

When R^3 in formula I is F, Cl, Br, I, N_3, CN, C≡CH, OH, OCH_3 or CH_2O it may have either cis-configuration or trans-configuration relative the hydroxymethyl function at position 4'.

Preferred compounds of the formula I are:

(a) A is 

(b) A is 

(c) R^3 at position 3' and the hydroxymethyl group at position 4' have the trans-configuration

(d) R^1 is CH_3 or C_2H_5

(e) X is O or CH_2

(f) X is O

(g) R^2 is H

(h) R^2 constitutes together with R^3 a carbon-carbon bond

(i) R^3 is H, F, N_3, OH, OCH_3, or CH_2OH or constitutes together with R^2 a carbon-carbon bond

(j) R^3 is H, F, or N_3

(k) the combination of (a), (c), (d) and (e) above

(l) the combination of (a), (c), (d), (e), (g) and (i) above

(m) the combination of (a), (c), (d), (f), (g) and (j) above

(n) the combination (a), (c), (d), (e) and (h) above

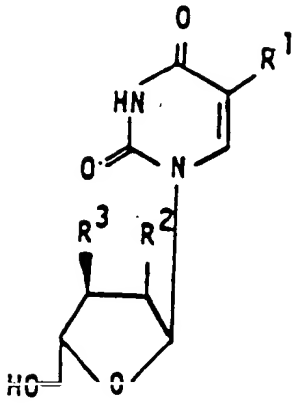
(o) the combination (b), (c), (d) and (e) above

(p) the combination (b), (c), (d), (e), (g) and (i) above

(q) the combination (b), (c), (d), (f), (g) and (j) above

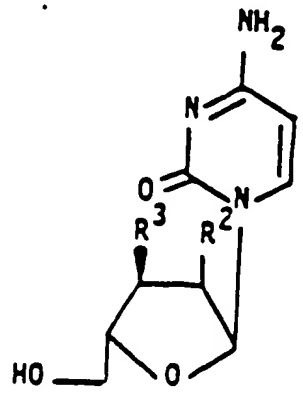
(r) the combination (b), (c), (d), (e) and (h) above

Examples of preferred compounds are:



R^1 is CH_3; R^2 is H; R^3 is H
R^1 is CH_3; R^2 is H; R^3 is OH
R^1 is CH_3; R^2 is H; R^3 is OCH_3
R^1 is CH_3; R^2 is H; R^3 is CH_2OH
R^1 is CH_3; R^2 is H; R^3 is F
R^1 is CH_3; R^2 is H; R^3 is N_3
R^1 is CH_3; R^2 and R^3 constitute together a carbon-carbon bond

R^1 is C_2H_5; R^2 is H; R^3 is H
R^1 is C_2H_5; R^2 is H; R^3 is OH
R^1 is C_2H_5; R^2 is H; R^3 is OCH_3
R^1 is C_2H_5; R^2 is H; R^3 is CH_2OH
R^1 is C_2H_5; R^2 is H; R^3 is F
R^1 is C_2H_5; R^2 is H; R^3 is N_3
R^1 is C_2H_5; R^2 and R^3 constitute together a carbon-carbon bond



R^2 is H; R^3 is H
R^2 is H; R^3 is OH
R^2 is H; R^3 is OCH_3
R^2 is H; R^3 is CH_2OH
R^2 is H; R^3 is F
R^2 is H; R^3 is N_3
R^2 and R^3 constitute together a chemical bond

In all the examples of preferred compounds R^3 at position 3' and hydroxymethyl at position 4' have the trans-configuration.

In clinical practice the nucleosides of the formula I will normally be administered orally, by injection or by infusion in the form of a pharmaceutical preparation comprising the active ingredient in the form of the original compound or optionally in the form of a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier which may be a solid, semi-solid or liquid diluent or an ingestible capsule. The compound may also be used without carrier material. As examples of pharmaceutical preparations may be mentioned tablets, dragées, capsules, granulates, suspensions, elixirs, syrups, solutions etc. Usually the active substance will comprise between 0.05 and 20 % for preparations intended for injection and between 10 and 90 % for preparations intended for oral administration.

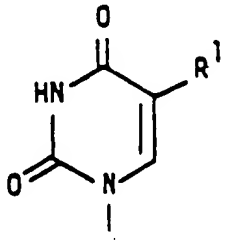
In the treatment of patients suffering from retrovirus, especially HIV, or hepatitis B virus infections, it will be preferred to administer the compounds by any suitable route including the oral, parenteral, rectal, nasal, topical and vaginal route. The parenteral route includes subcutaneous, intramuscular, intravenous and sublingual administration. The topical route includes buccal and sublingual administration. The dosage at which the active ingredients are administered may vary within a wide range and will depend on various factors such as the severity of the infection, the age of patient etc., and may have to be individually adjusted. As a possible range for the amount of the compounds of the invention or a physiologically acceptable salt thereof to be administered per day may be mentioned from about 10 mg to about 10 000 mg, pre-

ferentially 100 - 500 mg for intravenous administration and preferentially 100 - 3000 mg for oral administration.

Examples of pharmaceutically acceptable salts of the compounds of formula I include base salts, e.g. derived from an appropriate base, such as alkali metal (e.g. sodium), alkaline earth metal (e.g. magnesium) salts, ammonium and NX_4^+ (wherein X is C_{1-4} alkyl). Physiologically acceptable salts of a hydrogen atom or an amino group include salts of organic carboxylic acids such as acetic, lactic, gluconic, citric, tartaric, maleic, malic, panthothenic, isethionic, succinic, oxalic, lactbionic and succinic acids; organic sulfonic acids such as methanesulfonic, ethanesulfonic, benzenesulfonic, p-chlorobenzenesulphonic and p-toluenesulfonic acids and inorganic acids such as hydrochloric, hydriodic, sulfuric, phosphoric and sulfamic acids. Physiologically acceptable salts of a compound of an hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+, NH_4^+, and N (wherein X is a C_{1-4} alkyl group).

Those compounds of the formula I which are novel are summarized as compounds of the formula I with the provisos that

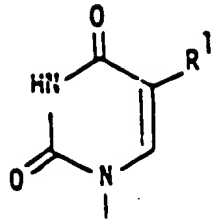
1. when A, X, R^2 and R^3 are combined as follows:

A is  ;

X is O;
R^2 is H;
R^3 is OH;

then R^1 is $-CH=CH_2$, $-CH=CH-CH_3$, $-CH_2-CH=CH_2$, $-C(=CH_2)-CH_3$, or cyclopropyl;

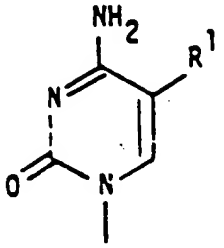
2. when A, X, R^2 and R^3 are combined as follows:

A is  ;

X is O;
R^2 is H;
R^3 is N_3;

then R^1 is H; alkyl containing 2-3 carbon atoms, $-CH=CH_2$; $-CH=CH-CH_3$; $-CH_2-CH=CH_2$; $-\overset{\overset{CH_2}{\|}}{C}-CH_3$; $-C\equiv CH$; or cyclopropyl;

3. when A, X, R^2 and R^3 are combined as follows:

A is  ;

X is O;
R^2 is H;
R^3 is OH;

then R^1 is alkyl containing 1-3 carbon atoms, $-CH=CH_2$; $-CH=CH-CH_3$; $-CH_2-CH=CH_2$; $-\overset{\overset{CH_2}{\|}}{C}-CH_3$; or cyclopropyl.

The administered compounds may also be used in therapy in conjunction with other medicaments such as 9-[(2-hydroxy-1-(hydroxymethyl)ethoxy)-methyl]guanine, 9-(2-hydroxyethoxymethyl)guanine (acyclovir), 2-amino-9-(2-hydroxyethoxymethyl)purine, interferon, e.g., ∝-interferon, interleukin II, and phosphonoformate, or in conjunction with immune modu-

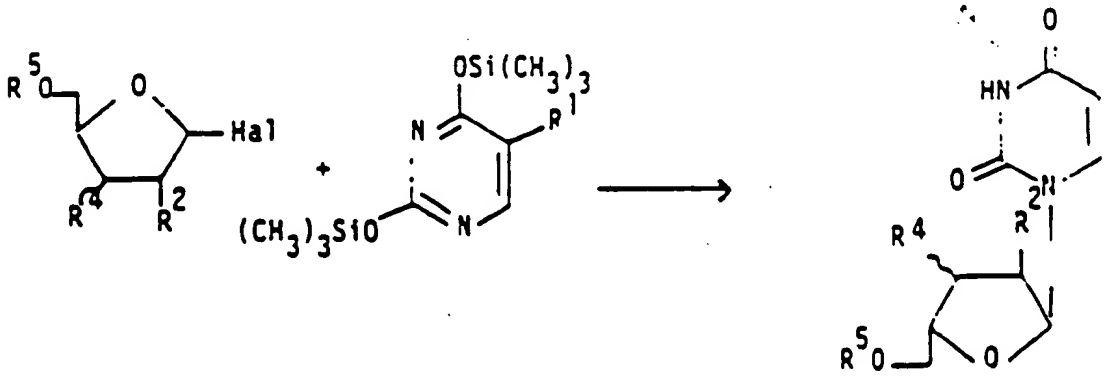
lating therapy including bone marrow or lymphocyte transplants or me cations such as levamisol or thymosin which would increase lymphocyt numbers and/or function as is appropriate.

Methods of preparation

The compounds of the invention may be prepared by one of the followi general methods, constituting a further aspect of the invention.

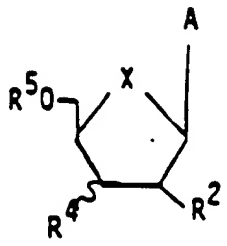
A. Condensing a glycoside as comprised in formula I, where the hydr groups may be optionally protected, to the N-1 position of a pyrimid derivative, corresponding to radical A in formula I according to kno methods described in the literature, followed by separation of the α-anomer and removal of any protecting group(s). Such methods are described for example in "Basic Principles in Nucleic Acid Chemistry' Vol. 1 (Academic Press, 1974, Ed. P.O.P.Ts'o), in "Nucleoside Analog Chemistry, Biology and Medical Applications" (Pharma Press, 1979, Eds. R.T. Walker, E. De Clercq and F. Eckstein) and in Nucleic Acids Research Vol. 12, 1984, pages 6827 - 6837 (A.J. Hubbard, A.S. Jones a R.T. Walker). An example of such a method is given for

the case of a uracil base analogue:

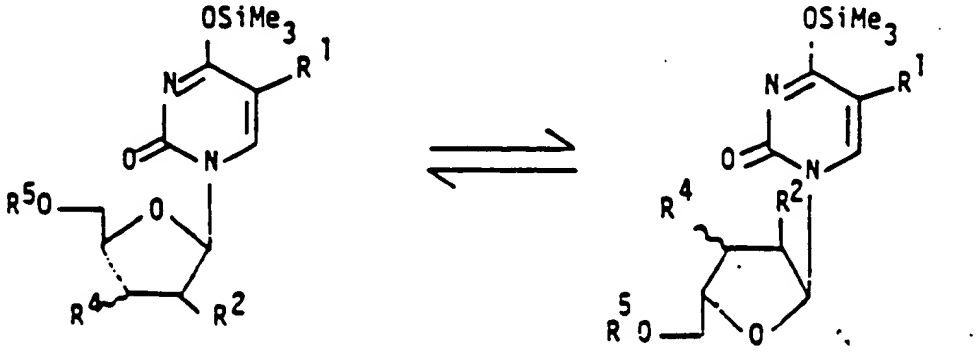


wherein R^4 is H, F, Cl, Br, I, N_3, CN, C≡CH, OR^5, OCH_3 or CH_2OR^5, R^5 a protecting group, of which a great variety is known, and examples of which are p-toluoyl, acetyl, trityl, benzyl. R^1 and R^2 are as defined above.

B. Anomerization of a β-anomer of the formula

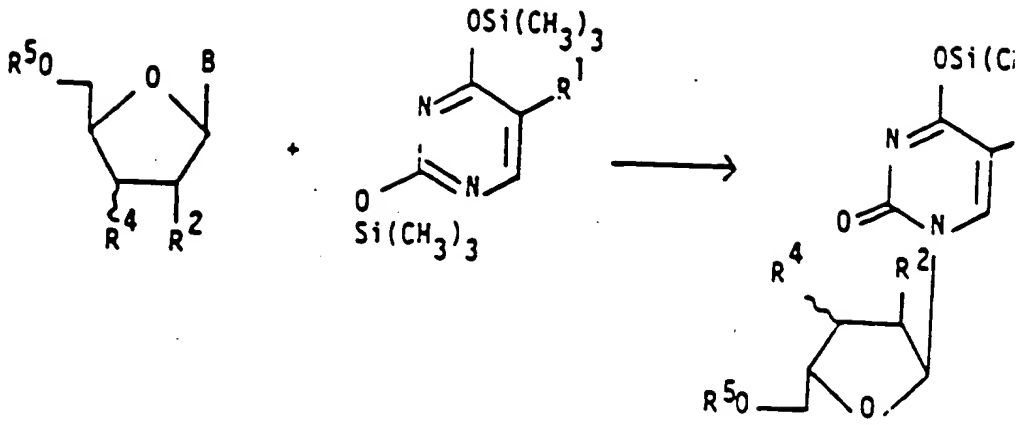


wherein A, X, and R^2 are as defined above, R^4 is H; F; Cl; Br; I; N_3; CN; OR^5; OCH_3; or CH_2OR_5; wherein R^5 is H or a hydroxy-protecting group to a mixture of α- and β-anomers, whereafter the α-anomer is separated and any protecting groups removed. The anomerization may be performed by known methods, e.g. with an optionally protected β-nucleoside, for example a silylated nucleoside, with a catalyst, such as for example trimethylsilyl trifluoromethanesulfonate



R^1, R^2, R^4 and R^5 are as defined above.

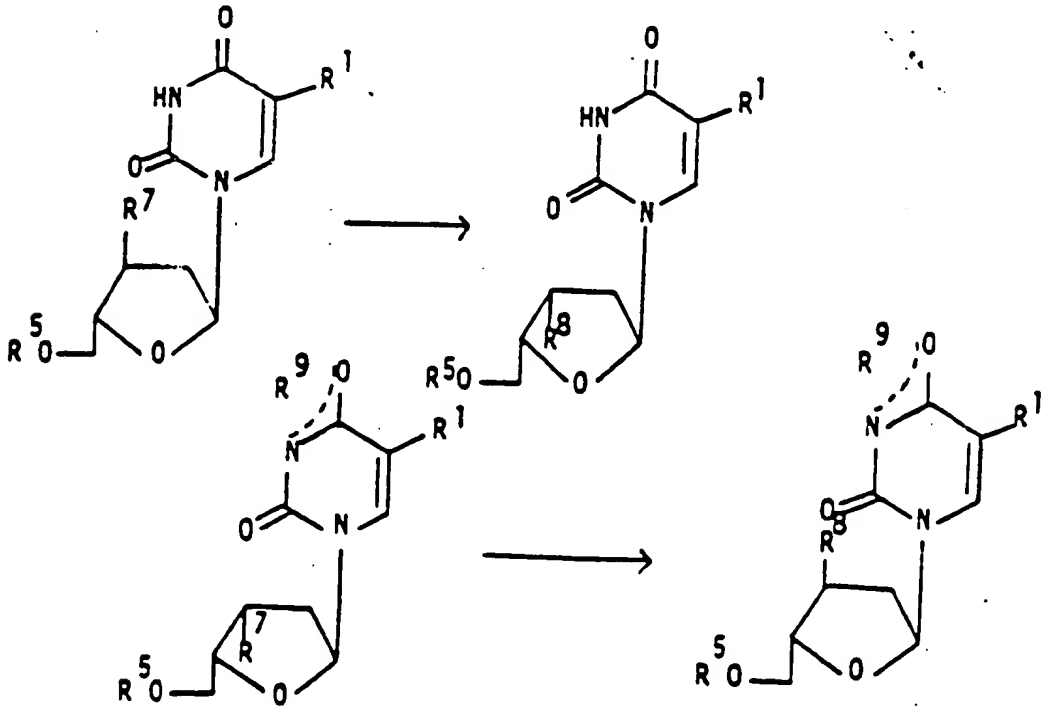
C. A transglycosylation reaction whereby the sugar moiety forming a bond, α- or β-, to one nucleoside base, is transferred to the desired pyrimidine base. The reaction is performed with a catalyst such as for example trimethylsilyl trifluoromethanesulfonate, and is followed by separation of the products and deprotection.

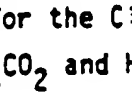


+ other products

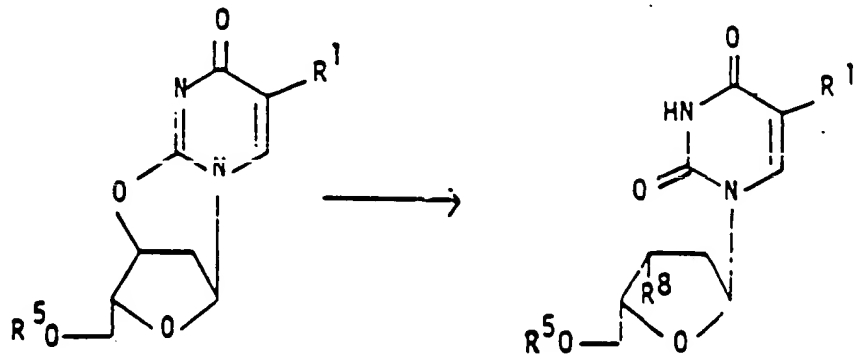
wherein R^1, R^2, R^4 and R^5 are as defined above. The radical B is a midine or purin base, the choice of which is not critical.

D. Introduction of the functional group R^3, or a precursor of R^3, the nucleoside α-anomer by substitution of a suitable leaving grou followed by deprotection.



R^1 and R^5 are as defined above, R^7 is a good leaving group such as for example trifluoromethanesulfonyloxy, R^8 is F, Cl, Br, I, N_3, CN, OCH_3 and synthos for the C≡CH, OH and CH_2OH groups, such as for example $C\equiv C\text{-}Si(CH_3)_3$, CH_3CO_2 and  . R^9 is a suitable protecting group

An alternative way for introduction of the R^8 function is by reaction the 2,3'-anhydro α-anomer.



wherein R^1, R^5 and R^8 are as defined above.

The principles of methods A-D above are applicable to the synthesis of both uridine and cytidine analogues of formulas I and II, although the formulas illustrating the reactions only depict uridine analogues.

E. Converting the uracil moiety of the 5-substituted or unsubstituted α-uridine compounds to a cytosine moiety of the corresponding α-cytidine analogues. This is carried out by conventional methods, the principles of which have been described for example by W.L. Sung (J. Chem. Soc. Chem. Commun. 1981, p. 1089 and J. Organic Chemistry 1982, volume 47, pages 3623 - 3628) and by P. Herdewijn et al. (J. Medicinal Chemistry 1985, volume 28, pages 550 - 555).

The following examples will further illustrate the invention.

Preparation of intermediate products

A. Preparation of 3'F-3'-deoxy-5'-O-acetylthymidine (VSB423)

3'F-3'-deoxythymidine 45 mg (0.184 mmol) in acetic anhydride (2.0 mL) was heated with stirring in an oil bath at 80° for 7 hrs. The solutio was evaporated in vacuo and the residual acetic anhydride and acetic acid were removed by several additions and reevaporations with benzen toluene (1:1). The residue was used without further purifications.

Preparation of compounds of the invention

Example 1. Preparation of 1-(3-F-2,3-dideoxy-α-D-ribofuranosyl)thymi (VSA 419) (Method B)

Thymine 23 mg (0.18 mmol) and 3'F-3'-deoxy-5'-O'-acetylthymidine was suspended in acetonitrile (1.2 mL) and N,O-Bis (trimethylsilyl)-aceta- mide (0.35 mL) was added. The mixture was stirred at room temperature for 1.5 hrs. Trimethylsilyl trifluoromethanesulfonate (0.05 mL) was added. After stirring at room temperature for 192 hrs, the mixture was poured under stirring into a 1:1 (v/v) mixture of 20 ml of 10 % aqueou $KHCO_3$-ethyl acetate. Two phases were separated and the water phase was extracted with ethyl acetate (3 x 10 mL). The combined ethyl acetate phase was filtered and evaporated in vacuo. The residue was dissolved dichloromethane-ethyl acetate 1:1 and applied to a column of silica ge and the column was eluated with dichloromethane-ethyl acetate 1:1 to give 28 mg (53 %) starting material (VSB 423) (Rf 0.37 on TLC silicage CH_2Cl_2-EtoAc 1:1) and 18 mg (34 %) of 1-(3-F-2,3-dideoxy-5-O-acetyl- -α-D-ribofuranosyl)thymine (VSB 424) (Rf 0.29 on TLC silica gel CH_2Cl_2-EtoAc 1:1).

NMR (CD_3OD) δ1.95 (s, 3H, CH_3-5), 2.12 (s, 3H, CH_3CO), 2.3-3.0 (m, 2H H-2'a,b), 4.15 (d, 2H, J4',5'=4.4 Hz, H-5'a,b), 4.81 (dt, 1H, J3'F,4'=30.0 Hz, J4',5'=4.6 Hz, H-4'), 5.23 (dd, 1H, J3'F,3'=53.7 Hz, J2',3'=5.0, H-3'), 6.36 (d, 1H, J1',2'=7.57 Hz, H-1'), 7.27 (d, 1H, J H-6, CH_3=1.47, H-6)

^{13}C(CD_3OD) δ12.80 (CH_3), 20.87 ($\underline{C}H_3CO$), 39.40 (d, J=20.8 Hz, C-2'), 63.37 (d, J=12.2 Hz, C-5'), 84.65 (d, J=24.4 Hz, C-4'), 86.50 (s, C-1') 93.82 (d, J=178 Hz, C-3'), 111.12 (C-5), 135.07 (d, J=6.1 Hz, C-6), 150.48 (C-2), 163.68 (C-4), 170.30 ($CH_3\underline{C}O$).

The compound VSB 424 (16 mg) was dissolved in saturated methanolic ammonia (5 mL) and left at room temperature overnight. The solution was evaporated and the residue was treated with acetone-benzene (1:4) to give crystals of the desired compound, VSA 419 (9.4 mg, 69 %) UV λmax (H_2O) 269 nm.

NMR (DMSO-d6) ^1H δ1.79 (d, 3H, J CH_3, H-6=1.2 Hz CH_3), 2.16-2.90 (m, 2H, H-2'), 3.2-3.6 (m, 2H, H-5'), 4,61 (dt, 1H, J3'F,4'=23.4 Hz, J4',5'= ~4 Hz, H-4'), 5.06 (t, 1H, J5',OH=5.6 Hz, OH), 5.32 (dd, 1H, J3'F,3'=54.2 Hz J2'3'=4.9 Hz, H-3'), 6.18 (dd, 1H, J1'2'=7.7 Hz and 2.1 Hz, H-1'), 7.39 (d, 1H, J CH_3, H-6=1.2 Hz, H-6)
^{13}C (DMSO-d6) δ12.46 (CH_3), ~39 (C-2'), 61.17 (d, J=11.0 Hz, C-5'), 85.85 (C-1'), 87.15 (d, J=20.8 Hz, C-4'), 94.75 (d, J=173 Hz, C-3'), 109.15 (C-5), 135.63 (d, J=6.1 Hz, C-6), 150.53 (C-2), 163.95 (C-4)

Example 2. Preparation of 1-(3-F-2,3-dideoxy-α-D-ribofuranosyl)--5-propyluracil (VSA 409) (Method C)

5-Propyluracil (56 mg) and 3'-F-3'deoxythymidine (47 mg) were suspended in acetonitrile (1.2 mL) and N,O-Bis (trimethylsilyl) acetamide (0.35 mL) was added. The mixture was stirred at room temperature for 1.5 hrs. Trimethylsilyl trifluoromethanesulfonate (0.05 mL) was added. After stirring at room temperature for 138 hrs, the mixture was evaporated in vacuo and added to H_2O (0.5 mL), filtered and washed with H_2O (0.5 mL). The combined water phase was applied to a C_{18}-column (HPLC) and eluted with methanol-water (35:65), at a rate of 7.0 ml/min. The β-anomer eluted after 12.9 min, and the desired α-anomer, VSA 409, after 18.0 min. Yield 9.3 mg (18 %), UV λ max (H_2O) 269 nm, MS M^+272 (10 %), 154 (100 %), 119 (76 %).

Example 3. Preparation of 1-(3-F-2,3-dideoxy-α-D-ribofuranosyl)-5-ethyluracil (VSA 411) (Method C)

5-Ethyluracil (51 mg) and 3'F-3'-deoxythymidine (48 mg) were sus
in acetonitrile (1.2 mL) and N,O-Bis (trimethylsilyl) acetamide (0.35 mL) was added. The mixture was stirred at room temperature 1.5 hrs. Trimethylsilyl trifluoromethanesulfonate (0.05 mL) was a After stirring at room temperature for 161 hrs, the mixture was e porated in vacuo, and added to water (0.5 mL), filtered and washe water (0.5 mL). The combined water phase was applied to a C_{18}-col (HPLC) and eluted with methanol-water (1:3) at a rate of 8.0 ml/m β-anomer eluted after 12.3 min and the desired α-anomer, VSA 41 after 16.4 min. Yield 13.1 mg (26 %). UV λ max (H_2O) 267.5 nm. MS (9 %), 140 (100 %), 119 (67 %).

Example 4. Preparation of 1-(2-deoxy-α-D-ribofuranosyl)-5-isopro uracil (VSA 175) (Method A)

5-Isopropenyluracil (4.3 g), hexamethyldisilazane (50 ml), chloro· trimethylsilane (1 ml) and ammoniumsulfate (catalytic amount) were heated at reflux for 2.5 hrs. Excess of solvent was evaporated in and the residual bis-silylated 5-isopropenyluracil (8.4 g) was dis in dichloroethane (50 ml) and added to 2-deoxy-3,5-di-O-p-toluoyl-D-erythro-pentosyl chloride (11.0 g) in dichloroethane (150 ml) al containing molecular sieves (4 Å, 15 g). The suspension was stirre room temperature overnight, after which it was filtered and the so was evaporated. The residue was redissolved in dichloromethane whi washed with saturated aq $NaHCO_3$ and H_2O, dried over Na_2SO_4 and con trated to a volume of about 70 ml. A precipitate formed which was filtered off, dichloromethane was evaporated from the filtrate and residue was subjected to chromatography on silica gel columns elute with hexane/ethylacetate/dichloromethane (5/5/3), to give 1-(2-deox 3,5-di-O-p-toluoyl-α-D-ribofuranosyl)-5-isopropenyluracil (VSA 174 2.64 g (Thin layer chromatography, silica gel, solvent system as ab Rf=0.5).

Sodium metal (0.25 g) was dissolved in dry methanol (263 ml), compound VSA 174 (2.64 g) was added and the solution was stirred at room temperature overnight, after which water (35 ml) was added. The solution was neutralized with an ion exchanger (Dowex H^+ 50Wx2), filtered and the solvent was evaporated. The residue was washed with hexane and purified by chromatography on a column of silica RP18 eluted with 50 % aq methanol to give 1-(2-deoxy-α-D-ribofuranosyl)-5-isopropenyluracil. (TLC silica RP8, 50 % aq methanol, Rf=0.5).

Biological tests

Test I. Effect of compounds of the formula I on HIV in H9 cells

Materials and methods: HIV infection of H9 cells

H9 cells, 10^5 cells per well on a 24 well plate, suspended in 2 ml RPMI-medium containing 10 % fetal calf serum, 100 µg/ml penicillin, 10 µg/ml streptomycin sulfate and 2 µg/ml polybrene are exposed to HIV ($HTLV\text{-}III_B$) and different concentrations of the test compounds. The plates are incubated at 37°C in 5 % CO_2 for 6 - 7 days. The contents in each well is then homogenized with a pipette and transferred to a centrifuge tube. After centrifugation for 10 min at 1500 rpm the supernatent is removed and the cell pellet is analyzed by fixing in methanol on glass plates. Human HIV positive serum diluted 1:80 or 1:160 is added and incubated for 30 min at 37°. The plate is then washed with phosphate-buffered saline (PBS) containing Ca^{2+} and Mg^{2+}. Sheep antihuman conjugate (FITC) is added and after a new incubation the plate is again washed with PBS. Contrast staining is done with Evans blue and after drying the frequency of HIV antigen containing cells is determined in a microscope. The test result is shown in Table 1.

Table 1. Concentration (μM) for 50 % inhibition (IC_{50}) of human immu deficiency virus multiplication in cell culture

Compounds	IC_{50}(μM)
1-(3-fluoro-2,3-dideoxy-α-D-ribofuranosyl)--5-ethyluracil (VSA 411)	0.1
1-(3-fluoro-2,3-dideoxy-α-D-ribofuranosyl)--5-propyluracil (VSA 409)	2.5
1-(2-deoxy-α-D-ribofuranosyl)-5-ethyluracil (VIP 289)	10

It is seen in Table 1 that the tested compounds are active inhibitors HIV virus multiplication.

Test II. Cellular toxicity

H_9 cells, $2x10^7$ cells per plate, are incubated in RPMI-1640 medium cor taining 10 % fetal calf serum, 70 mg/l penicillin, 100 mg/l streptomyc and 10 mM hepes, in absence or precence of test compounds. The number cells per plate is determined after 48 hrs. Cells incubated in absence of test compound then underwent two cell division cycles.

F5000 cells, which are human embryo cells, $1x10^5$ cells per plate, are incubated in Eagle's minimal essential medium, supplemented with Earle salts, non-essential amino acids, 10 % fetal calf serum, 10 mM hepes, 70 mg/l penicillin and 100 mg/l streptomycin, in absence or presence o test compounds. The number of cells per plate is determined after 48 hrs. Cells incubated in absence of test compounds underwent one cel division cycle. The results are given as TC_{50}, which is the concentration of a compound which gives 50 % inhibition of cell multiplication.

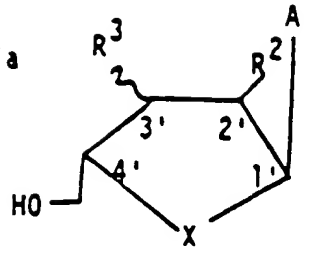
Table 2. Cellular toxicity and H9 and F5000 cells

Compound	TC_{50} (μM) H9	F5000
1-(3-fluoro-2,3-dideoxy-α-D-ribofuranosyl)-5-ethyluracil (VSA 411)	400	500
1-(3-fluoro-2,3-dideoxy-α-D-ribofuranosyl)-5-methyluracil (VSA 419)		250
1-(2-deoxy-α-D-ribofuranosyl)-5-ethyluracil (VIP 289)		1000

It is seen in Table 2 that the test compounds exhibit TC_{50} values which vastly exceed the concentration IC_{50} according to Table 1 to 50 % inhibition of HIV virus multiplication.

Claims

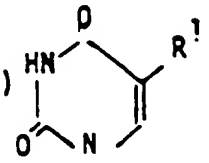
1. A compound of the formula



I

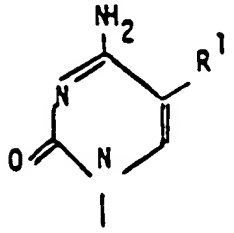
wherein the radicals A, X, R^1, R^2, and R^3 are defined as follows.

A : (a)



or

(b)



X: (a) O
(b) S
(c) CH_2

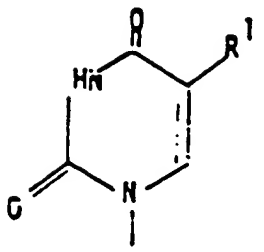
R^1: H; alkyl containing 1-3 carbon atoms, including cyclopropyl;

$-CH=CH_2$; $-CH=CH-CH_3$; $-CH_2-CH=CH_2$;
$-C(=CH_2)-CH_3$; $-C\equiv CH$

R^2: H; or R^2 constitutes together with R^3 a carbon - carbon bond

R^3: H; F; Cl; Br; I; N_3; CN; $-C\equiv CH$; OH; OCH_3; CH_2OH; whereby when R^3 in formula I is F; Cl; Br; I; N_3 ; CN; $C\equiv CH$; OH; OCH_3 or CH_2OH it may have either cis-configuration or trans-configuration relative to the hydroxymethyl function at position 4', or R^3 constitutes together with R^2 a carbon - carbon bond, and therapeutically acceptable salts thereof, with the following provisos (a) - (c):

(a) When A, X, R^2 and R^3 are combined as follows:

A is 

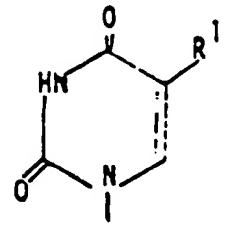
X is O ;

R^2 is H ;

R^3 is OH ; whereby OH at position 3' and hydroxymethyl at position have the trans-configuration.

then R^1 is $-CH=CH_2$, $-CH=CH-CH_3$,
$-CH_2-CH=CH_2$, $-\overset{\overset{CH_2}{\|}}{C}-CH_3$, or cyclopropyl

(b) When A, X, R^2 and R^3 are combined as follows:

A is 

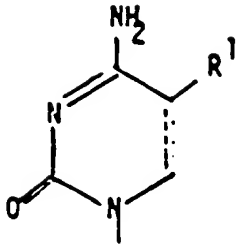
X is O;

R^2 is H;

R^3 is N_3; whereby N_3 at position 3' and hydroxymethyl at position 4' have the trans-configuration;

then R^1 is H; alkyl containing 2-3 carbon atoms or including cycloprop:
$-CH=CH_2$; $-CH=CH-CH_3$; $-CH_2-CH=CH_2$;
$-\overset{\overset{CH_2}{\|}}{C}-CH_3$; or $-C\equiv CH$;

(c) When A, X, R^2 and R^3 are combined as follows:

A is 

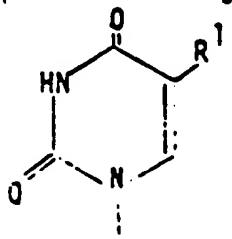
X is O;

R^2 is H;

R^3 is OH; whereby OH at position 3' and hydroxymethyl at position 4' have the trans-configuration;

then R^1 is alkyl containing 1-3 carbon atoms including cyclopropyl, $-CH=CH_2$; $-CH=CH-CH_3$; $-CH_2-CH=CH_2$; or $-C(=CH_2)-CH_3$.

2. A compound according to claim 1 wherein A is



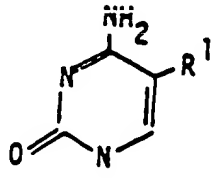
and R^1, R^2, R^3 and X are as defined in claim 1.

3. A compound according to claim 2 wherein R^1 is H, CH_3 or C_2H_5.

4. A compound according to claim 3 wherein R^3 is H; OH; OCH_3; CH_2OH; F; N_3 or R^2 and R^3 together constitute a carbon-carbon bond; and X is O or CH_2.

5. A compound according to claim 4 wherein R^3 at position 3' and hydroxymethylat position 4' have the transconfiguration.

6. A compound according to claim 1 wherein A is



and R^1, R^2, R^3 and X are as defined in claim 1.

7. A compound according to claim 6 wherein R^1 is H; CH_3 or C_2H_5.

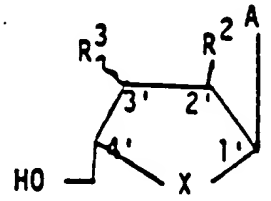
8. A compound according to claim 7 wherein R^1 is H.

9. A compound according to claim 8 wherein R^3 is H; OH; OCH_3 ; CH_2OH; F; N_3 or R^2 and R^3 together constitute carbon-carbon bond; and X is O or CH_2.

10. A compound according to claim 9 wherein

R^3 at position 3' and hydroxymethyl at position 4' have the trans configuration.

11. A compound of the formula



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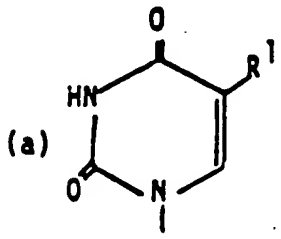
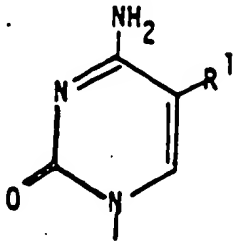
wherein the radicals A, X, R^1, R^2, and R^3 are defined as follows:

A :





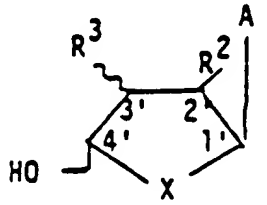
X : (a) O
(b) S
(c) CH_2

R^1: H; alkyl containing 1-3 carbon atoms including cyclopropyl; $-CH=CH_2$; $-CH=CH-CH_3$; $-CH_2-CH=CH_2$; $-C(=CH_2)-CH_3$; $-C\equiv CH$

R^2: H; or R^2 constitutes together with R^3 a carbon - carbon bond

R^3: H; F; Cl; Br; I; N_3; CN; $-C\equiv CH$; OH; OCH_3; CH_2OH; and when R^3 is F; Cl; Br; I; N_3 ; CN; $C\equiv CH$; OH; OCH_3 or CH_2OH it may have either the cis-configuration or trans-configuration relative to the hydroxymethyl function at position 4', or R^3 constitutes together with R^2 a carbon - carbon bond, and therapeutically acceptable salts thereof, for use in therapy.

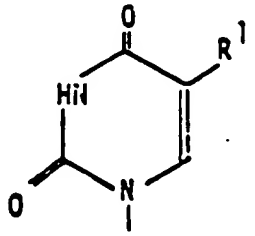
12. A pharmaceutical composition comprising as active ingredient a compound of the formula



I

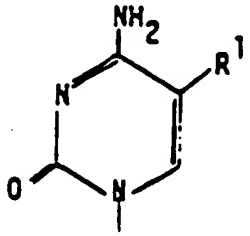
wherein the radicals A, X, R^1, R^2, and R^3 are defined as follows:

A : (a)



or

(b)



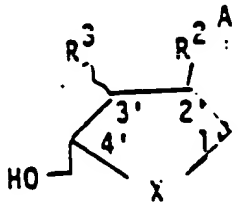
X : (a) O
(b) S
(c) CH_2

R^1: H; alkyl containing 1-3 carbon atoms including cyclopropyl
$-CH=CH_2$; $-CH=CH-CH_3$; $-CH_2-CH=CH_2$; $-C(=CH_2)-CH_3$; $-C\equiv CH$

R^2: H; or R^2 constitutes together with R^3 a carbon - carbon bond

R^3: H; F; Cl; Br; I; N_3; CN; $C\equiv CH$; OH; OCH_3; CH_2OH; and when R^3 is F; Cl; Br; I; N_3 ; CN; $C\equiv CH$; OH; OCH_3 or CH_2OH it may have either the cis-configuration or trans-configuration relative to the hydroxymethy function at position 4', or R^3 constitutes together with R^2 a carbon carbon bond, and therapeutically acceptable salts thereof.

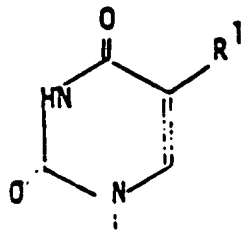
13. A compound of the formula



I

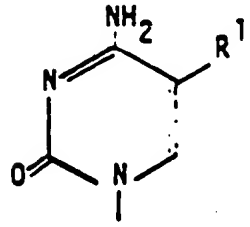
wherein the radicals A, X, R^1, R^2 and R^3 are defined as follows:

A : (a)



or

(b)



X : (a) O
(b) S
(c) CH_2

R^1: H; alkyl containing 1-3 carbon atoms including cyclopropyl;
$-CH=CH_2$; $-CH=CH-CH_3$; $-CH_2-CH=CH_2$; $-C-CH_3$; $-C\equiv CH$

R^2: H; or R^2 constitutes together with R^3 a carbon - carbon bond

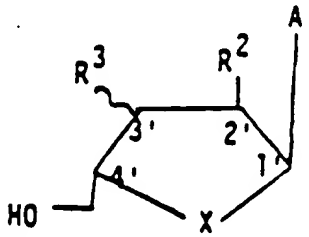
R^3: H; F; Cl; Br; I; N_3; CN; -C≡CH; OH; OCH_3; CH_2OH; when R^3 is F; Cl; Br; I; N_3 ; CN; C≡CH; OH; OCH_3 or CH_2OH it may have either cis-configuration or trans-configuration relative to the hydroxymethyl function at position 4', or R^3 constitutes together with R^2 a carbon - carbon bond, and therapeutically acceptable salts thereof, for use in the manufacture of a medicament for therapeutic and/or prophylactic treatment of infections caused by a retrovirus or by hepatitis B virus.

14. A compound according to claim 13 for use in the therapeutic treatment of infection in man caused by HIV virus.

15. A method for the therapeutic and/or prophylactic treatment of infections in mammals and man caused by a retrovirus including HIV or hepatitis B virus, by administrering to a host in need of such treatment an efficient amount of a compound of the formula I as defined in claim 11.

16. A method according to claim 15 for the therapeutic treatment of infections in man caused by HIV virus.

17. A process for the preparation of a compound of the formula

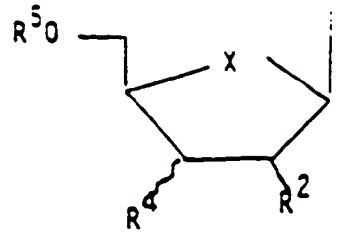


I

or a therapeutically acceptable salt thereof, wherein A, X, R^2 , and R^3 are as defined in claim 1, by

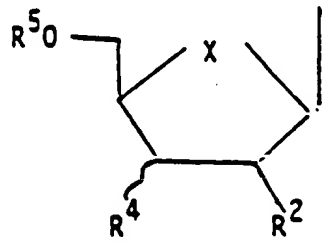
A. Condensing a glycoside as comprised in formula I

to the N-1 position of a pyrimidine derivative corresponding to radical A in Formula I, whereafter the α-anomer of compound I thus formed is separated and any protecting groups removed;



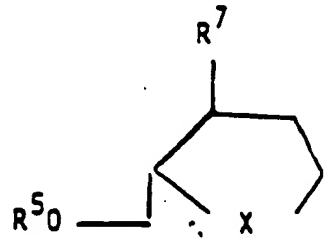
wherein A, X, R^2, R^4 and R^5 are as defined above, to a mixture of α a
β- anomers, whereafter the α-anomer is separated and any protecting gro
removed;

C. Transglycosylation of a nucleoside of the formula



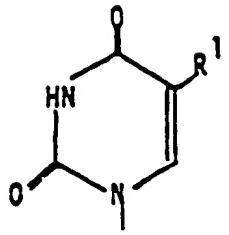
where X, R^2, R^4 and R^5 are as defined above, and B is a pyrimidine c
purin base, to the formation of a nucleoside containing the pyrimidine
radical A as defined above, whereafter the α-anomer is separated and any
protecting groups removed;

D. Substitution of the radical R^7 in a compound of the formula

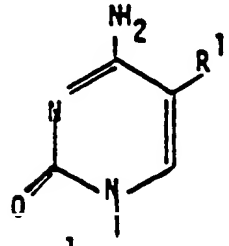


wherein A, X and R^5 are as defined above, and R^7 is a leaving group,
with a radical R^3, whereafter any protecting groups are removed;

E. Conversion of the uracil moiety



in a compound of the formula I to a cytosine moiety



wherein R^1 is as defined above,

whereafter the compound of the formula I thus obtained if desired is converted to a therapeutically acceptable salt.

International Application No

I. CLASSIFICATION OF SUBJECT MATTER

According to International Patent Classification (IPC) or to both National Classification and IPC 4

C 07 H 19/06, 19/073; C 07 D 239/46, 405/04, 409/04; A 61 K 31/70

II. FIELDS SEARCHED

Minimum Documentation Searched

Classification System	Classification Symbols
IPC 2,3,4	C 07 H 19/02, 19/04, 19/06, 19/073; A 61 K 31/70
IPC 1	C 07 d 51/50, 51/52
US Cl	536:23, 24; 424:180; 514:23, 42, 43, 49, 50

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched

SE, NO, DK, FI classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	Journal of Medicinal Chemistry, Vol 17, No 3, 1974, T Kulikowski et al, "5-Alkylpyrimidine Nucleosides. Preparation and Properties of 5-Ethyl-2'-deoxycytidine and Related Nucleosides", see p. 269-273	1-14, 17
X	EP, A, 0 217 580 (THE WELLCOME FOUNDATION LIMITED) 8 April 1987 & EP, 0196185 DE, 3608606 GB, 2181128 JP, 62103100	1-14, 17
X	DE, A, 3 002 197 (ROBUGEN GMBH PHARMAZEUTISCHE FABRIK ESSLINGEN A.N.) 23 July 1981	1-14, 17
X	DE, A, 3 045 375 (ROBUGEN GMBH PHARMAZEUTISCHE FABRIK ESSLINGEN A.N.) 1 July 1982	1-14, 17
X	DE, A, 3 229 169 (ROBUGEN GMBH PHARMAZEUTISCHE FABRIK) 9 February 1984	1-14, 17

.../...

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of the International Search Report
1988-07-11	1988 -07- 22
International Searching Authority	**Signature of Authorized Officer**
Swedish Patent Office	Gunilla Claesson

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 15 & 16 because they relate to subject matter not required to be searched by this Authority, namely:

Method for treatment of the human or animal body by therapy.

2. [X] Claim numbers ..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

*) Claims 1-14 and 17 has been searched incompletely.

According to PCT, Art. 15(3) the search has been limited to what has been shown in the working examples, namely compounds of the formula 1 wherein X is O.

3. [ ] Claim numbers ..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING :

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	US, A, 3 116 282 (THE UPJOHN COMPANY) 31 December 1963	1-14, 17
X	Chemical Abstracts, Vol 102 (1985), abstract No 7013q, Chem. Pharm. Bull. 1984, 32(4), 1441-50 (Eng)	1-14, 17
X	Chemical Abstracts, Vol 92 (1980), abstract No 208903d, Vopr. Virusol. 1979, (6), 603-6 (russ)	1-14
X	Chemical society, London. Journal. Perkin trans. I, 1978, P J Barr et al, "The Synthesis of Nucleosides derived from 5-Ethynyluracil and 5-Ethynyl-cytosine" see p. 1263-1267	1-14, 17
X	DE, A, 2 930 904 (GAURI, KAILASH KUMAR) 19 February 1981	1-14, 17
X	DE, A, 2 918 260 (ROBUGEN GMBH PHARMAZEUTISCHE FABRIK ESSLINGEN A.N.) 27 November 1980	1-14, 17
X	EP, A, 0 206 497 (THE WELLCOME FOUNDATION LIMITED) 30 December 1986 & JP, 61280500	1-14, 17
X	EP, A, 0 196 185 (THE WELLCOME FOUNDATION LIMITED) 1 October 1986 & DE, 3608606 EP, 0199451 JP, 61257925 US, 4724232 EP, 0217580 GB, 2181128 JP, 62103100.	1-14, 17
X	EP, A, 0 199 451 (THE WELLCOME FOUNDATION LIMITED) 29 October 1986 & JP, 61257926 EP, 0196185 DE, 3608606 JP, 61257925 US, 4724232	1-14, 17
X	US, A, 3 817 982 (VERHEYDEN ET AL) 18 June 1974	1-14, 17
X	US, A, 4 247 544 (BERGSTROM ET AL) 27 January 1981	1-14, 17
X	US, A, 4 267 171 (BERGSTROM ET AL) 12 May 1981	1-14, 17

.../...

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SEC ND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Cl
X	J. Carbohydrates.Nucleosides.Nucleotides, Vol. 5, No 3, 1978, E DeClerq et al, "Nucleoside analogs with selective antiviral activity", see p 187-224	1-14
X	FR, A, 2 040 177 (ROBUGEN GMBH) 22 January 1971	1-14, 1
X	DD, A, 75 084 (DR GERHARD ETZOLD ET AL) 5 August 1970	1-14, 1